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ORIGINAL RESEARCH

Mean Platelet Volume to Platelet Count Ratio Predicts Left Atrial Stasis in Patients with Non-Valvular Atrial Fibrillation

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Background: The mean platelet volume to platelet count ratio (MPV/PC) has been investigated in the diagnosis, prognosis and risk stratification in several diseases. However, the predictive role of MPV/PC in left atrial stasis (LAS) of non-valvular atrial fibrillation (NVAF) patients remains unknown.

Methods: A total of 217 consecutive NVAF patients undergoing transesophageal echocardiogram (TEE) evaluation were retrospectively enrolled. The demographic, clinical, admission laboratory and TEE data were extracted and analyzed. Patients were categorized into those with or without LAS. The associations between the MPV/PC ratio and LAS were assessed by multivariate logistic regression analysis.

Results: There were 24.9% (n = 54) patients with LAS according to TEE. Compared with patients without LAS, the MPV/PC ratio was significantly higher in those with LAS (5.6±1.6 vs 4.8±1.0, P < 0.001). After multivariable adjustment, higher MPV/PC ratio levels (OR 1.747, 95% CI 1.193–2.559, P = 0.004) were positively associated with LAS, with the optimal cut-point for LAS prediction of 5.36 (area under the curve, AUC = 0.683, sensitivity 48%, specificity 73%, 95% CI 0.589–0.777, P < 0.001). The stratification analysis showed that a significant positive correlation between MPV/PC ratio ≥5.36 and LAS in patients of male, younger (<65 years), paroxysmal AF, without history of stroke/TIA, CHA_2DS_2-VASc score ≥2, left atrial diameter (LAD) ≥40mm and left atrial volume index (LAVI) >34mL/m^2 (all P < 0.05).

Conclusion: Increasing MPV/PC ratio was associated with an increased risk of LAS, which was mainly reflected in the subgroups of male, younger (<65 years), paroxysmal AF, without history of stroke/TIA, CHA_2DS_2-VASc score ≥2, LAD ≥40mm and LAVI >34mL/m^2 patients.

Keywords: non-valvular atrial fibrillation, mean platelet volume to platelet count ratio, left atrial appendage thrombus, spontaneous echo contrast

Introduction

Nonvalvular atrial fibrillation (NVAF) is the most common cardiac arrhythmia, and predisposes to thrombus formation.[1] Among them, ischemic stroke is the predominant complication.[2] Hemodynamic abnormalities during AF episodes could cause blood stasis and thrombus formation in the left atrial (LA), especially in LA appendage (LAA).[3] Left atrial stasis (LAS), which manifests as LA thrombus (LAT) and/or spontaneous echo contrast (SEC) assessing by transesophageal echocardiography (TEE), progresses to thromboembolic events without appropriate anticoagulation therapy.[4] However, it is always accompanied with operational risk and patients' sufferings. Therefore, exploring some simple and noninvasive predictors for LAS in this earlier thromboembolic risk stage has attracted great interest.

Increased platelet activation and inflammatory response are important in the pathogenesis of AF, stimulation of coagulation cascade and thrombus formation.[5–7] The mean platelet volume (MPV), a marker of platelet activity, could be considered as a prognostic factor in a number of inflammatory diseases.[5,7] Furthermore, it is currently suggested that MPV may be a useful marker of the prediction for AF occurrence and LAS in NVAF.[8–10] Platelet count (PC), an indicator of platelet production, is also associated in inflammatory conditions. The inverse relationship between MPV and PC

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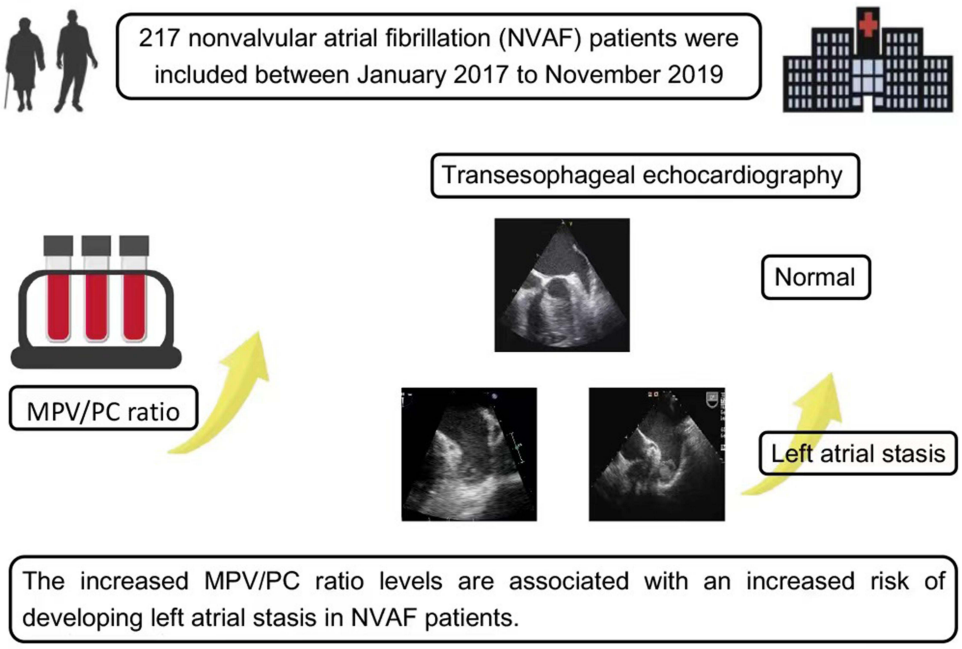
Graphical Abstract



physiologically will be disturbed in various pathologies (eg, coagulation), which suggests the need to interpret MPV and PC as a ratio rather than as independent variables.[7,11] Moreover, previous studies reported that the MPV/PC ratio was a superior indicator of platelet function compared to MPV or PC alone, with the possible explanation of that it may better represent the platelet activation and inflammatory reaction in several pathophysiologic states.[12] Although it has been identified as a predictor of postoperative prognosis in patients with coronary heart disease,[13,14] it remains unclear whether MPV/PC ratio could predict of LAS in NVAF. Therefore, the purpose of the present study was to address the predictive value of MPV/PC ratio in identifying LAS in patients with NVAF.

Materials and Methods

Study Population

We retrospectively enrolled consecutive hospitalized patients with NVAF who were referred to undergo transthoracic echocardiography (TTE) and TEE to "rule-out" LAT prior to radiofrequency catheter ablation (RFCA) at the department of cardiology, Beijing Friendship Hospital (Beijing, P.R. China) from January 2017 to November 2019. Participants meeting any of the following criteria were excluded: 1) history of structural heart disease, valvular abnormalities and cardiac surgery; 2) thromboembolic disease (left atrial thrombosis without anticoagulation therapy, ischemic stroke within 1 months, deep venous thrombosis, pulmonary embolism or left ventricular thrombus); 3) terminal illness (malignant tumours, end-stage hepatic or renal dysfunction); and 4) other diseases (hyperthyroidism, inflammatory disease or hematological disease) (Figure 1). After admission, oral anticoagulants and antiplatelet drugs were discontinued in all patients, and subcutaneous low-molecular-weight heparin was used twice per day.

The investigation complied with the Declaration of Helsinki. The protocol was approved by the Institutional Review Board of Beijing Friendship Hospital (No. 2022-P2-173-01, approved date: May 26, 2022), and all patients provided written informed consent.

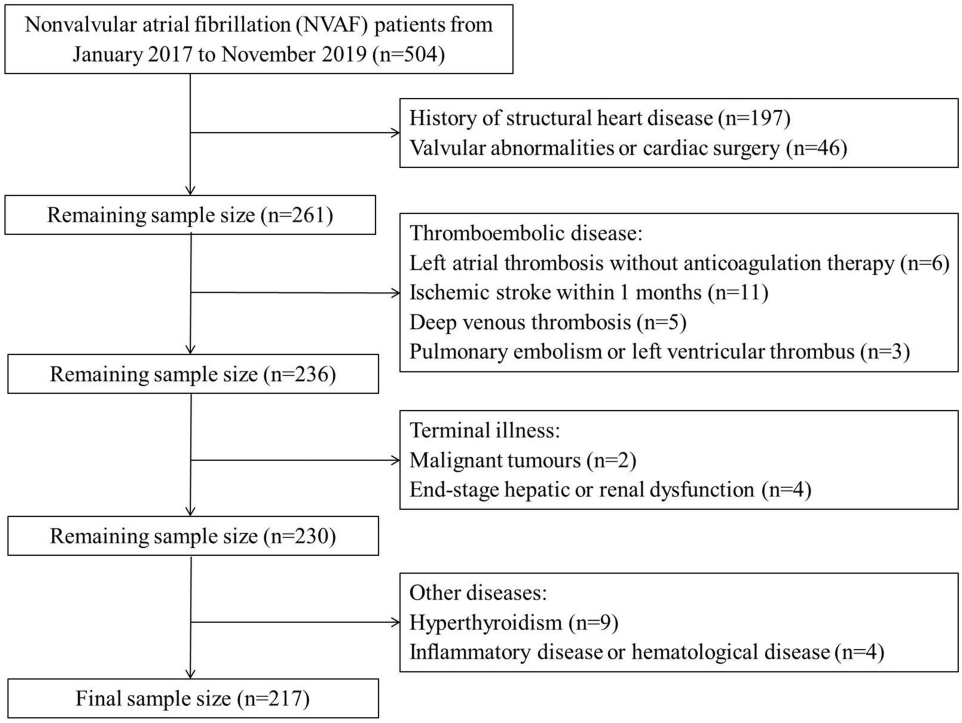


Figure 1 Flow chart of study participants.

Clinical Data Collection

The baseline characteristics with demographic, anthropometric, clinical, laboratory, echocardiographic data, and medication administration records of all patients were collected from medical records and analyzed. AF was classified as: 1) paroxysmal, defined as recurrent AF terminating within 7 days spontaneously; 2) persistent, including persistent AF and long-standing persistent AF, defined as any AF events lasting longer than 7 days or requiring termination by cardioversion. The CHA_2DS_2-VASc score was calculated for each patient.[3]

Laboratory Analysis

Peripheral blood samples were obtained from the basilic vein the morning after admission (after overnight fast). Complete blood cell counts including the MPV and PC were measured using the SF-3000 analyzer (Sysmex Corporation, Kobe, Japan) within 2 hours of blood sample collection. All samples were assayed in the laboratory of our hospital, and laboratory personnel were blinded to the clinical status. The normal ranges of MPV and PC were 7–13 fL and $125–350\times10^9$/L, respectively. The MPV/PC ratio was calculated by a formula "[MPV value/(PC/10^9)]×100" which was utilized by Tuysuz ME.[15]

Echocardiography Evaluation

All enrolled subjects underwent TTE and TEE after admission routinely. All parameters were determined by 2 experienced physicians. Any difference was resolved by a third independent observer. TTE was performed with a cardiovascular ultrasound system (IE 33 Elite, Royal Philips, Netherlands or Vivid E9, General Electric Company, US) to measure LA diameter (LAD), left ventricular ejection fraction (LVEF) and other parameters determined from the parasternal M-mode or 2D images. Left atrial volume index (LAVI) was defined as left atrial volume (LVA) standardized for body surface area (BSA). In detail, three LADs were measured from images optimized for the LA at end systole. D1 is the anterior-posterior (A-P) dimension measured perpendicular to the aortic root long axis in the parasternal long axis view, D2 is the superior inferior (S-I) dimension measured between the mitral annulus and the back wall of the left atrium, and D3 is the medial lateral (M-L) dimension orthogonal to D2 measured from the apical 4-chamber. LAV was

calculated using the formula: (D1(A-P)×D2(S-I)×D3(M-L))×(0.523).[16] The BSA was calculated by the Mosteller formula.[17]

After informed consent, TEE was performed in all patients using an ultrasound system equipped with a TEE transducer (X7-2t, Philips Healthcare) under local anesthesia by lidocaine hydrochloride spray. Left atrial cavity and LAA were carefully evaluated in multiple planes. LAT was defined as a circumscribed intracavitary echo-dense mass showing acoustic characteristics distinct from the surrounding endocardium and pectinate muscles observed in multiple planes.[18] SEC was defined as dynamic "smoke-like" echoes with characteristic chaotic swirling during the cardiac cycle, with the severity of SEC 3+ or 4+ as reported previously.[19]

Statistical Analysis

All statistical analyses were performed by SPSS 19.0 (SPSS Inc., Chicago, Illinois, USA). Continuous values were expressed as mean±SD and categorical variables as n (%). The differences between continuous values were assessed using an unpaired Student's *t*-test for normally distributed continuous variables, a Mann–Whitney *U*-test for skewed data. The chi-squared test or Fisher's exact test was used to compare categorical variables if necessary. Receiver operating characteristic (ROC) curve analysis was performed to assess the ability of MPV/PC ratio to predict LAS in the study population and to identify the optimal cut-off value (upper left corner of ROC as point with the highest sum of sensitivity and specificity), with the area under the curve (AUC) for determining the predictive value. To identify the independent predictors of LAS, the forward stepwise multivariate logistic regression analysis was performed, which included variables with $p < 0.10$ from the univariate logistic regression or of clinical importance. A two-tailed P value <0.05 was considered statistically significant, and odds-ratios (OR) were given with the 95% confidence interval (CI).

Results

Baseline Characteristics of Patients

A total of 217 patients (53.0% males) with NVAF aged 66.4±8.7 years were enrolled to measure MPV and PC in a blood sample drawn and underwent TEE to exclude LAS. The baseline and echocardiographic characteristics are summarized in Table 1. More than half of them (71.9%, n = 156) were identified as having hypertension, 25.8% (n = 56) had diabetes mellitus, 25.3% (n = 55) had dyslipidemia, 17.5% (n = 38) had previous history of stroke/TIA, 10.6% (n = 23) had vascular disease and 2.3% (n = 5) had congestive heart failure.

Among them, 54 patients (24.9%, mean age of 66.4±8.9 years) were identified with LAS during TEE examination. Patients with LAS were more likely to be male sex, and had higher CHA_2DS_2-VASc score, higher incidence of persistent AF and previous stroke/TIA, larger LAD, LAVI and LAA width, lower LVEF and slower LAA emptying velocity ($P < 0.05$, respectively).

Relationships Between LAS and MPV/PC Ratio

The mean MPV/PC ratio was 5.0±1.2 of all the study participants. Patients with LAS had a significantly higher MPV/PC ratio than those without LAS (5.6±1.6 vs 4.8±1.0, $P < 0.001$). Univariate and multiple logistic regression analyses were used to assess the association between surrogate clinical and echocardiographic parameters and LAS (Table 2). In univariate analysis, the significant predictive effect was observed in the MPV/PC ratio (OR 1.772, 95% CI 1.288–2.437, $P < 0.001$). Male sex ($P = 0.047$), persistent AF ($P < 0.001$), CHA_2DS_2-VASc score ($P < 0.001$), previous stroke/TIA ($P = 0.046$), LAD ($P < 0.001$), LAVI ($P < 0.001$), LAA width ($P = 0.010$) and LAA emptying velocity ($P < 0.001$) were among the other predictors of LAS. After adjustment for these factors and age, the ORs and 95% CIs for LAS showed a significant gradual increase at higher levels of CHA_2DS_2-VASc score, LAVI and the MPV/PC ratio (all P for trend <0.05). The per one increment of CHA_2DS_2-VASc score, LAVI and the MPV/PC ratio was significantly associated with 53%, 17% and 75% higher risks for LAS, respectively (OR 1.536, 95% CI 1.066–2.213, $P = 0.021$; OR 1.177, 95% CI 1.014–1.365, $P = 0.032$ and OR 1.747, 95% CI 1.193–2.559, $P = 0.004$, respectively).

Table 1 Baseline Characteristics of Patients with or Without LAS (LAT and/or SEC)

Variable	Total (n=217)	LAS (n=54)	Without LAS (n=163)	*P*-value
Age, year	66.4±8.7	66.4±8.9	66.4±8.7	0.981
Male, n (%)	115 (53.0%)	36 (66.7%)	79 (48.5%)	0.020
BMI, Kg/m^2	25.9±4.7	25.7±4.8	26.4±4.2	0.360
AF				
Persistent AF, n (%)	64 (29.5%)	29 (53.7%)	39 (21.5%)	<0.001
AF history, months	44.8±4.8	51.4±5.5	42.9±4.5	0.469
Laboratory data				
Creatinine, μmol/L	70.4±15.3	71.3±14.9	70.1±16.3	0.106
Fibrinogen, mg/dL	2.8±0.7	3.0±0.9	2.8±0.7	0.703
CHA_2DS_2-VASc score	2.7±1.4	3.2±1.4	2.5±1.4	0.009
Congestive heart failure, n (%)	5 (2.3%)	2 (3.7%)	3 (1.8%)	0.600
Hypertension, n (%)	156 (71.9%)	37 (68.5%)	119 (73.0%)	0.525
Diabetes mellitus, n (%)	56 (25.8%)	18 (33.3%)	38 (23.3%)	0.145
Previous stroke/TIA, n (%)	38 (17.5%)	15 (27.7%)	23 (14.1%)	0.022
Vascular disease, n (%)	23 (10.6%)	6 (11.1%)	17 (10.4%)	0.888
Dyslipidemia, n (%)	55 (25.3%)	18 (33.3%)	37 (22.7%)	0.119
Echocardiographic parameters				
LAD, mm	41.4±5.4	44.6±5.0	40.3±5.2	<0.001
LVEDD, mm	50.0±4.6	50.0±5.3	50.0±4.4	0.868
LVEF, %	64.5±8.2	62.2±8.0	65.2±8.2	0.040
LAA width, mm	17.9±4.2	19.4±4.3	17.4±4.1	0.008
LAA length, mm	29.0±5.6	30.3±5.3	28.1±5.7	0.324
LAA emptying velocity (cm/s)	47.3±14.1	39.5±14.6	50.2±12.8	<0.001
Antiplatelet & anticoagulant drugs, n (%)				
Aspirin, n (%)	51 (23.5%)	10 (18.5)	41 (25.2%)	0.276
Warfarin, n (%)	31 (14.3%)	11 (20.4%)	20 (12.3%)	
NOAC, n (%)	25 (11.5%)	7 (13.0%)	18 (11.0%)	
MPV/PC ratio	5.0±1.2	5.6±1.6	4.8±1.0	<0.001

Abbreviations: AF, atrial fibrillation; LAA, left atrial appendage; LAD, left atrial dimension; LAS, left atrial stasis; LAT, left atrial thrombus; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NOAC, new oral anticoagulant; SEC, spontaneous echo contrast; TIA, transient ischaemic attack; MPV/PC ratio, the ratio of the mean platelet volume to platelet count.

Table 2 Univariate and Multivariate Regression Analysis for LAS (LAT and/or SEC)

Variables	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age	1.000 (0.961–1.042)	0.981	0.952 (0.897–1.009)	0.100
Male sex	2.098 (1.010–4.359)	0.047	0.528 (0.194–1.437)	0.211
Persistent AF	4.394 (2.092–9.228)	<0.001	2.152 (0.838–5.526)	0.111
CHA_2DS_2-VASc score	1.569 (1.239–1.988)	<0.001	1.612 (1.130–2.299)	0.008
Previous stroke/TIA	2.417 (1.018–5.742)	0.046	1.209 (0.357–4.089)	0.761
LAD	4.653 (2.204–9.826)	<0.001	2.031 (0.783–5.270)	0.145
LAA width	3.306 (1.300–7.909)	0.010	2.079 (0.717–6.031)	0.178
LAA emptying velocity	0.936 (0.906–0.967)	<0.001	0.969 (0.931–1.009)	0.130
MPV/PC ratio	1.772 (1.288–2.437)	<0.001	1.693 (1.168–2.454)	0.005

Abbreviations: AF, atrial fibrillation; CI, confidence interval; OR, odds ratio; LAA, left atrial appendage; LAD, left atrial dimension; LAS, left atrial stasis; LAT, left atrial thrombus; MPV/PC ratio, the ratio of the mean platelet volume to platelet count; SEC, spontaneous echo contrast; TIA, transient ischaemic attack.

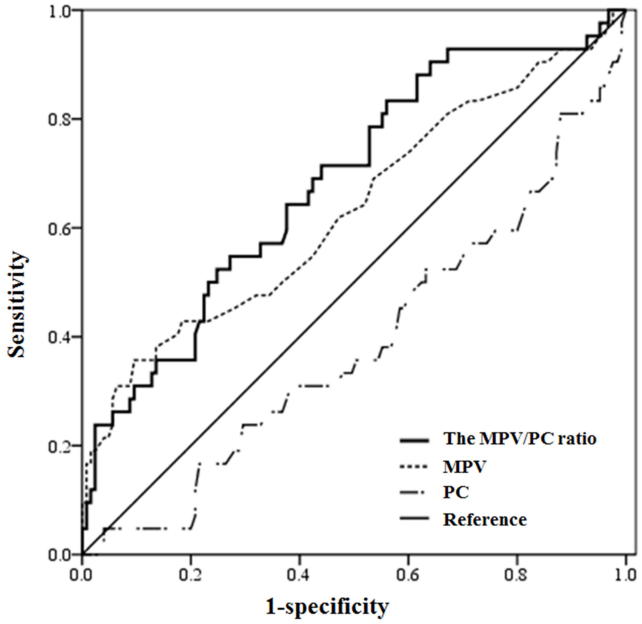


Figure 2 Receiver operating characteristic curve for MPV/PC ratio and MPV or PC alone in predicting LAS in patients with NVAF. The MPV/PC ratio was a better predictor than either MPV or PC alone.

ROC Analysis of the MPV/PC Ratio and LAS

ROC curve analysis was performed to measure the predictive ability of the MPV/PC ratio to the risk of LAS in patients with NVAF (Figure 2). The AUC of the MPV/PC ratio was 0.683 (95% CI 0.589–0.777, P < 0.001), with a sensitivity of 48% and a specificity of 73%. The predictive value of the MPV/PC ratio was superior to either MPV or PC alone, which the AUC were 0.632 (95% CI 0.528–0.737, P = 0.01) and 0.387 (95% CI 0.287–0.488, P = 0.029), respectively. The optimal cut-off point for the MPV/PC ratio predicting LAS was 5.36. In patients with the MPV/PC ratio ≥5.36, the incidence of LAS was significantly higher than those <5.36 [40.6% (28/69) vs 17.6% (26/148), P < 0.001].

Subgroup Analyses by Potential Effect Modifiers

A stratified analysis of potential covariates was conducted in this survey. In MPV/PC ratio ≥5.36 group, the incidences of LAS were higher in males and patients with paroxysmal AF, without history of stroke/TIA, CHA_2DS_2-VASc ≥2 and LAD ≥40mm, regardless of age or LAVI (all P < 0.05, Figure 3 and Table 3). After adjusting for potential confounders,

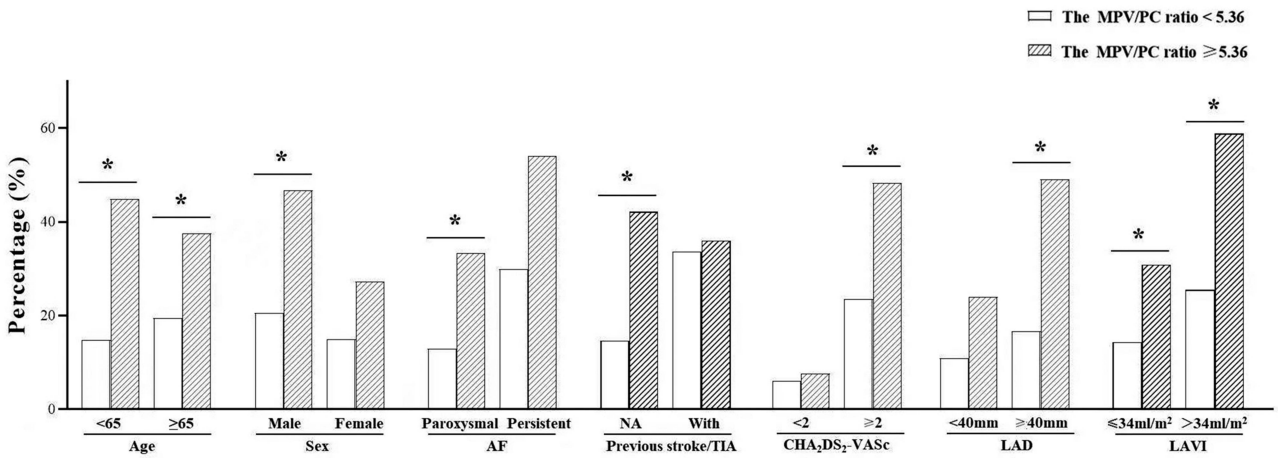


Figure 3 Proportion of the participants with LAS stratified by age, sex, types of AF, previous history of stroke/TIA, CHA_2DS_2-VASc score, LAD and LAVI. *P < 0.05.
Abbreviations: AF, atrial fibrillation; LAD, left atrial dimension; LAVI, left atrial volume index; TIA, transient ischaemic attack; MPV/PC ratio, the ratio of the mean platelet volume to platelet count.

Table 3 Incidences of LAS in Different Potential Covariates

Age	<65 (n=90, 41.5%)			≥65 Years (n=127, 58.5%)		
	LAS(+)	LAS(-)	P	LAS(+)	LAS(-)	P
MPV/PC<5.36 MPV/PC≥5.36	3 19	16 52	0.385	5 27	25 70	0.218
Sex	Male (n=115, 53.0%)			Female (n=102, 47.0%)		
	LAS(+)	LAS(-)	P	LAS(+)	LAS(-)	P
MPV/PC<5.36 MPV/PC≥5.36	14 22	54 25	0.003	12 6	68 16	0.210
AF	Paroxysmal (n=152, 70.0%)			Persistent (n=65, 30.0%)		
	LAS(+)	LAS(-)	P	LAS(+)	LAS(-)	P
MPV/PC<5.36 MPV/PC≥5.36	11 14	97 30	0.001	16 13	25 11	0.236
Previous stroke/TIA	Without (n=179, 82.5%)			With (n=38, 17.5%)		
	LAS(+)	LAS(-)	P	LAS(+)	LAS(-)	P
MPV/PC<5.36 MPV/PC≥5.36	29 10	121 19	0.070	10 5	20 3	0.223
LAD	<40mm (n=91, 41.9%)			≥40mm (n=126, 58.1%)		
	LAS(+)	LAS(-)	P	LAS(+)	LAS(-)	P
MPV/PC<5.36 MPV/PC≥5.36	8 3	65 15	0.450	18 25	57 26	0.004
CHA_2DS_2-VASc	<2 (n=63, 29.0%)			≥2 (n=154, n=71.0%)		
	LAS(+)	LAS(-)	P	LAS(+)	LAS(-)	P
MPV/PC<5.36 MPV/PC≥5.36	3 1	47 12	1.000	23 27	75 29	0.002

Abbreviations: AF, atrial fibrillation; LAD, left atrial dimension; LAS, left atrial stasis; TIA, transient ischaemic attack; MPV/PC ratio, the ratio of the mean platelet volume to platelet count.

a strong positive correlation between the MPV/PC ratio ≥5.36 and the prevalence of LAS was mainly reflected in the subgroups of younger than 65 (OR 5.799, 95% CI 1.121–36.500, P = 0.041), male gender (OR 4.234, 95% CI 1.088–16.480, P = 0.037), paroxysmal AF (OR 2.831, 95% CI 1.106–7.245, P = 0.030), without previous history of stroke/TIA (OR 2.685, 95% CI 1.076–7.385, P = 0.046), CHA_2DS_2-VASc score ≥2 (OR 2.770, 95% CI 1.006–7.632, P = 0.049), LAD ≥40mm (OR 3.050, 95% CI 1.885–8.246, P = 0.039), as well as LAVI >34mL/m^2 (OR 5.462, 95% CI 1.098–29.906, P = 0.044) (Figure 4).

Discussion

In this study cohort with NVAF patients, we determined that higher levels of the MPV/PC ratio (≥5.36) were associated with a higher prevalence of LAS (LAT and/or LASEC) after multivariable adjustments. Second, the positive association of the higher level of MPV/PC ratio for incidence of LAS was mainly reflected in the subgroups of males, younger (<65 years), paroxysmal AF, without previous history of stroke/TIA, CHA_2DS_2-VASc score ≥2, LAD ≥40mm and LAVI >34mL/m^2 patients.

Accumulative data documented that LAS, including LAT and SEC, is strongly associated with thromboembolism and adverse outcomes in NVAF patients.[20] TEE was recommended to evaluate the risk of thromboembolism previous to procedures.[3,21] The latest research has shown that the platelet plays an important role in thrombus

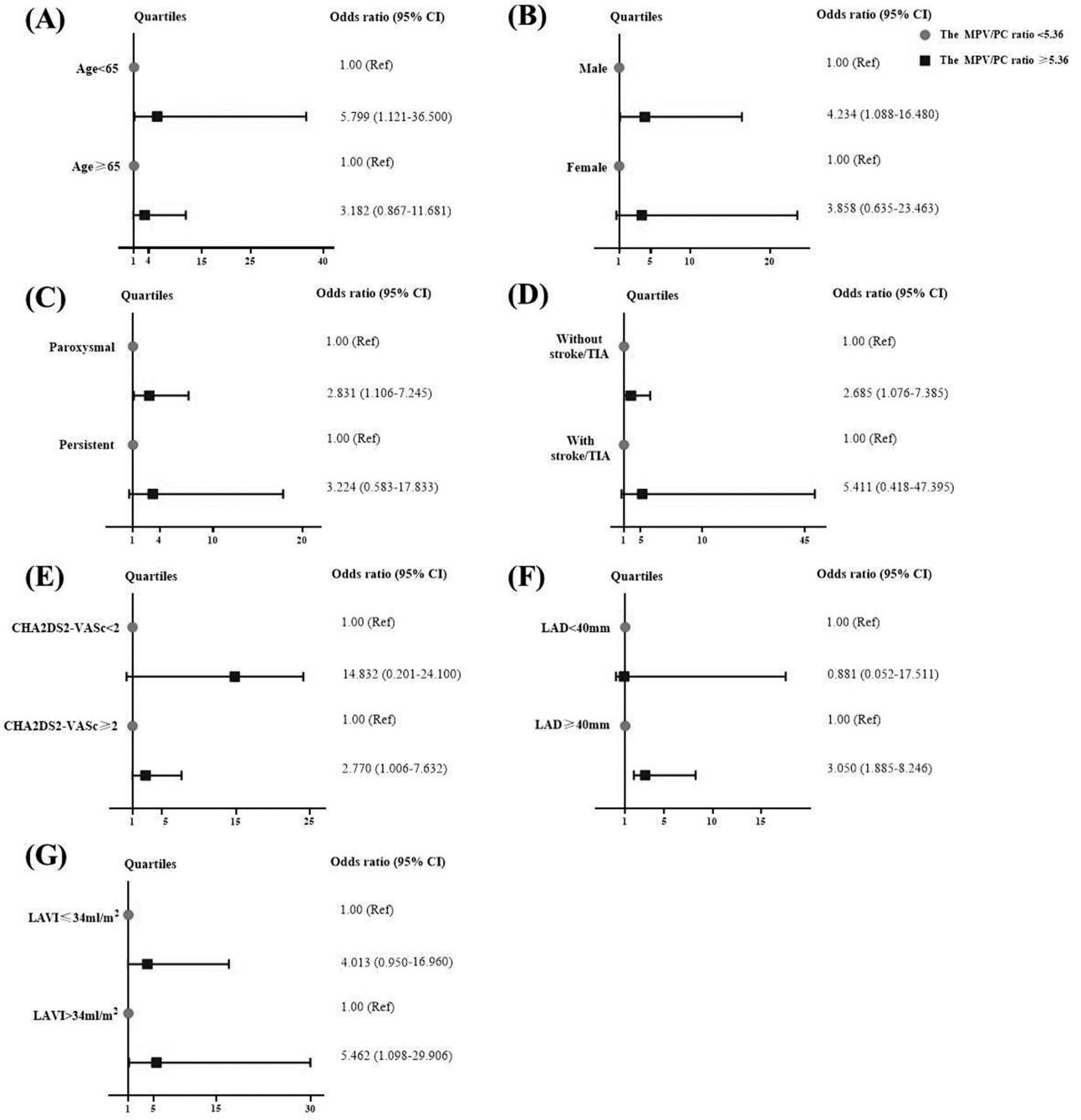


Figure 4 Effects of the MPV/PC ratio on LAS by prespecified subgroups. Prespecified subgroups of interest in this analysis are age (**A**), sex (**B**), types of AF (**C**), previous history of stroke/TIA (**D**), CHA_2DS_2-VASc score (**E**), LAD (**F**) and LAVI (**G**).

formation[7] and its parameters (eg, MPV and PC) are able to assess by a routine complete blood count analysis simply and inexpensively.

MPV, a precise measurement of platelet dimension, has been demonstrated to reflect platelet activity. Although the predictive of prognostic values of MPV in coronary heart disease were contradictory, more extensive research is needed to eliminate this complexity.[22] Emerging evidence supports MPV is a biomarker predicting the risk of occurrence of AF and ischemic stroke in AF patients, and as a guide for prescription of anticoagulation and rhythm-control therapy.[5] MPV was considered as a quick and reliable guide in the assessment of LAS in patients with symptomatic atrial fibrillation patients[8] and primary mitral regurgitation.[23] A recent case-control study showed that a high MPV, with the cutoff value

of >9.4 fl, is associated with an increased risk of stroke in AF patients.[24] Therefore, MPV was recommended to be added to the diagnostic criteria and risk stratification of AF.

There are only a few studies assessing the link of PC with AF. It was reported that there was a close relationship between lower PC level and the occurrence and poor prognosis of ischemic stroke and ischemic heart diseases.[25,26] Thus, the prognostic significance of lower PC should be focused on, especially in critical illness or major surgeries.[27] Despite significant heterogeneity among the studies, two meta-analysis and systematic reviews[9,28] recently indicated an inverse relationship between PC and the risk of new-onset and postoperative AF. However, no correlation between PC and the occurrence and prognosis of ischemic events (eg, stroke) was found and even a contradictory result was presented.[29] The controversial results may be partly explained by small sample size, insufficient exclusion criteria and different grouping methods.

In physiological conditions, MPV is inversely proportional to the PC, which reflects the tendency to maintain hemostasis by preserving a constant platelet mass.[11] It means that the increased production of platelets is accompanied by a reduction in their mean volume. Therefore, MPV and PC should be interpreted as a ratio rather than independent variables. The MPV/PC ratio has been investigated in the diagnosis, prognosis and risk characterization in various diseases, eg, myocardial infarction (MI), sepsis, and metabolic status of platelets in cardiac surgical patients.[13–15,30–32] Guenancia et al[33] suggested that a high MPV/PC ratio might help to identify acute MI patients at increased risk of in-hospital ischemic stroke. To our knowledge, the association of the MPV/PC ratio and NVAF has not been reported till now. In our study, we demonstrated that the MPV/PC ratios were significantly higher in patients with LAS than those without, and the elevated ratio was independently associated with LAS in multivariate analysis. Moreover, the MPV/PC ratio was superior to the MPV alone in terms of prediction in the present study, which was in line with study results in patients with MI.[13,14,32] However, the prevalence of LAS in our study was different from others,[8,18] mostly due to the differences among the enrolled subjects in these studies.

The mechanisms linking the MPV/PC ratio with LAS are not yet well elucidated. Increased platelet activation and inflammatory processes are considered as the possible mechanisms resulting in hypercoagulable state in AF.[6,7,34] The pathophysiological function for our finding may be as follows: higher MPV/PC ratio means higher MPV and lower PC. Higher MPV is enzymatically and metabolically more dynamic, and they exhibit greater prothrombotic potential and severe inflammatory reactions. Large platelets correlate with increased platelet aggregation and adhesion molecules expression, enhanced synthesis, release of thromboxane and β-thromboglobulin, undergo faster activation, as well as endothelial dysfunction, which results in hyperactivity and accelerates thrombus formation.[34,35] In addition, numerous inflammatory cytokines (eg, IL-1, IL-6 and TNF-α) related to higher MPV are also able to regulate thrombopoiesis and participate in thrombosis.[6] On the other hand, Bigalke et al[36] suggested that lower PC related to higher expression of inflammatory biomarkers and glycoprotein VI (GPVI) in acute coronary syndrome, which could enhance the process of platelet adhesion and thrombus information. All these alterations fulfill the Virchow's triad for thrombogenesis in NVAF.[37]

The association between the MPV/PC levels and LAS incidence was statistically significant for males and individuals with LAD ≥40mm, LAVI >34mL/m^2 or CHA_2DS_2-VASc score ≥2. The result may be driven by the sex difference in electrophysiological properties of the atria and greater the number of comorbidities in these subgroups.[18,38] However, a strong positive correlation between the MPV/PC ratio and the prevalence of LAS can be also observed in younger (<65 years), paroxysmal AF and without previous history of stroke/TIA. Chang SS et al[39] demonstrated that persistent AF and history of stroke/TIA were factors positively associated with OAC use in Chinese patients with AF. Therefore, the low proportions of OAC usage could possibly account for these differences.

In sum, high levels of the MPV/PC ratio were found in NVAF patients, and the MPV/PC ratio was independently associated with LAS in multivariate analysis. Our results add to the growing literature on clinical indicator and LAS development. Moreover, these data support that the MPV/PC ratio might improve risk stratification, through the subgroup analysis. However, a more precise mechanism needs to be investigated further.

Limitations

There were several potential limitations with the present study. Firstly, this study was a retrospective and cross-sectional study in our single center, and we only analyzed the correlation between the MPV/PC ratio and LAS without attempting to identify the causality or mechanisms. Secondly, the population might not represent the general AF population due to

the small sample size and sample selection bias. Therefore, large-scale perspective studies would be warranted to validate the predictive value of the MPV/PC ratio for LAS in different populations. Finally, other inflammatory factors, eg, C-reactive protein, neutrophil to lymphocyte ratio,[9] were not measured in the present study, whether they interacted with each other remained unknown.

Conclusion

The increased MPV/PC ratio levels were associated with an increased risk of developing LAS (LAT and/or LASEC) in patients with NVAF, and that the association was remained consistent in subgroups of males, younger (<65 years), paroxysmal AF, without previous history of stroke/TIA, CHA_2DS_2-VASc score ≥2, LAD ≥40mm and LAVI >34mL/m^2 patients. Larger prospective studies are still required to confirm and reveal clinical implications of the prediction value of the MPV/PC ratio for thromboembolism.

Abbreviations

AF, atrial fibrillation; AUC, area under the curve; BSA, body surface area; CI, confidence interval; LAA, left atrial appendage; LAD, left atrial dimension; LAS, left atrial stasis; LAT, left atrial thrombus; LAV, left atrial volume; LAVI, left atrial volume index; LVEDD, left ventricular end-diastolic dimension; LVEF, left ventricular ejection fraction; NOAC, new oral anticoagulant; NVAF, nonvalvular atrial fibrillation; OR, odds-ratio; RFCA, radiofrequency catheter ablation; SEC, spontaneous echo contrast; TEE, transesophageal echocardiography; TIA, transient ischaemic attack; MPV/PC ratio, the ratio of the mean platelet volume to platelet count.

Ethics Approval and Consent to Participate

This study was approved by the Institutional Review Board of Beijing Friendship Hospital, Capital Medical University, and written informed consent was obtained from all patients.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

All authors declare that they have no competing interests.

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